

LH-RH can also be assayed in *urine*. 1 – 2 percent of an injected dose is excreted within 8 hours. Basal excretion rates in normal human subjects are 15 – 60 ng/day. Urine LH-RH is immunochemically identical but chromatographically (on ion-exchange columns) different and evidence suggests that it is the des-glu¹-nonapeptide or des-glu¹, his²-octapeptide of LH-RH.

LH-RH has been detected and measured by radioimmunoassay in the *blood* of rats, rabbits, chickens,

sheep and human subjects. In man the levels in peripheral blood range between <0.25 pg/ml and 3.5 pg/ml. Levels of up to 10,000 pg/ml can be detected in the jugular vein of the ewe during the oestrous cycle. Ion-exchange chromatography of serum extracts from various species followed by radioimmunoassay suggests that circulating immunoreactive LH-RH is heterogeneous and 4 distinct components have been identified.

LH-RH in Paediatrics

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Secretion of gonadotropins before puberty has been considered a dormant function until measurable levels in plasma and urine were reported in young children by means of radioimmunoassay techniques (Johanson *et al.* 1969, Raiti *et al.* 1969). More detailed studies and reports on feedback of sex hormones in prepuberal children (Burr *et al.* 1970, Kehl *et al.* 1973) supported the earlier concept of the gonadostat already functioning before puberty with decreasing sensitivity for circulating sex hormones. Even with expanding insight into the complicated dependency of CNS, pituitary, and end organ for the maturation of the reproductive system in man the mechanism of puberty onset remains obscure (Root 1973, Visser 1973).

The purification and synthesis of the hypothalamic gonadotropin releasing factor (LH-RH) (Schally *et al.* 1971, Monahan *et al.* 1971) provides a new tool for the evaluation of physiological and pathological relations between CNS and pituitary (Job *et al.* 1972, Grumbach *et al.* 1972). At present it is still uncertain whether the prepuberal pituitary can be stimulated to adult secretion of FSH and LH by LH-RH (Kastin *et al.* 1972). Dose responses of graded infusions of LH-RH in prepuberal boys and girls have not been reported so far. With a reliable RIA for FSH and LH in children (Joel *et al.* 1973)

we found a distinct rise of the gonadotropins in prepuberal boys but no dose response after LH-RH (Hoe 471) in doses of 6.25 – 200 µg/m². In contrast prepuberal girls had a much higher rise of FSH with clear dose response while LH was comparable to boys. After puberty onset the starting levels of FSH were higher but were only moderately elevated after LH-RH with nearly no dose response. LH levels were less elevated at start but could be stimulated to a greater extent with more pronounced dose response. The interpretation of a sex dependent alteration in responsiveness and depletion of the pituitary during puberty will await more data on stimulation and feedback. Estrogens may play a role in prepuberal girls in triggering the more pronounced stimulation of FSH. The preponderance of LH after puberty onset may reflect the start of cyclic discharge and importance in adult females.

For the clinical evaluation of the CNS-pituitary axis in hypo- and hypergonadism in children first promising results have been published (Job *et al.* 1972, Roth *et al.* 1972). The group of constitutional delay of maturation can be clearly distinguished. Results for organical gonadotropin deficiency are more difficult to interpret (Grumbach 1972). In precocious puberty the LH-RH test may be useful for the diagnosis of true or pseudoprecocity but for the treatment with competitive LH-RH analogs also (Vale *et al.* 1972). Routine treatment which still is not entirely satisfactory would be another field of this test in paediatrics. (Literature on request.)

LH-RH in Ovarian-Insufficiency *

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The use of synthetic LH-RH permits the assessment of pituitary responsiveness and helps to differentiate

ovarian dysfunction originating in the pituitary from that originating in the hypothalamus and or in the central nervous system. In 100 patients with various types of ovarian insufficiency LH-RH-stimulation was done. The patients were classified according to their total gonadotrophin excretion: group 1: <2.4 IU II. IRP HMG/24 h, group 2:

* Supported by DFG, Sonderforschungsbereich -34-, "Endokrinologie".

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2.4–10 IU/24 h, group 3: 10–50 IU/24 h, group 4: >50 IU/24 h.

The results evidence a positive correlation between the functional status of the pituitary as indicated by the urinary gonadotrophin levels and the response to exogenous LH-RH as followed by plasma-levels of FSH and LH. Most of the patients with undetectable low urinary gonadotrophin levels failed to respond to LH-RH. The majority of patients with urinary gonadotrophin levels in the normal range, reacted promptly to exogenous LH-RH. Patients with primary ovarian failure and elevated gonadotrophin levels exhibit the most impressive response to exogenous LH-RH.

Further clinical studies were done to assess the therapeutic value of synthetic LH-RH in two aspects: 1. Stimulating of follicular maturation and 2. induction of ovulation in HMG stimulated ovaries. Exclusive administration of 100 to 200 μ g

LH-RH daily for 3 weeks did not result in any ovarian stimulation in amenorrhoeic women. In a group of amenorrhoeic patients in whom follicular maturation was achieved by HMG-stimulation LH-RH was administered when follicular activity was optimal as reflected by the estrogen plasma levels. Despite the fact that the plasma LH increased in 8 patients to ovulatory levels, ovulation presumably occurred in only 4 patients. HMG administration normally results in the maturation of a large number of follicles. Therefore it is obvious that those stimulated ovaries are rich in receptor sites for LH which eventually compete with those follicles which are ready for ovulation. In animal experiments it could be shown that it is not possible to release enough LH by LH-RH to saturate the receptor sites in HMG stimulated rat ovaries. This in contrast was possible with exogenous HCG. At the present we are studying the effect of LH-RH administration in patients with anovulatory cycles.

Diagnostic Use of TRH in Thyroid Disorders

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By measuring the TSH plasma levels before and 30 min after i.v. administration of synthetic TRH (short TRH test) and simultaneous estimation of thyroid hormone concentrations it is possible to get good informations about disturbances of the hypothalamo-pituitary-thyroid relationship. The TSH increment after TRH is abolished if a certain individually varying hormone concentration is exceeded or if the thyrotrophic pituitary cells are completely destroyed. Thereby the pituitary reacts rather sensitive in slight changes of hormone concentrations which might even not be detectable in blood ("subclinical" hyperthyroidism, "euthyroid" ophthalmopathy or "compensated" autonomous adenoma). The TRH test seems not to be suited for the evaluation of pituitary TSH reserve (e.g. in pituitary tumors), since there is quite often a normal TSH response in patients with advanced pituitary destruction and low serum levels of thyroid hormones. Furthermore the TSH peak levels after TRH are

delayed in some of these cases. Thus a differentiation of secondary hypothyroidism due to hypothalamic or pituitary disorders is rather difficult by the TRH test. On the other hand, even in very slight decrease of thyroid hormones ("subclinical" primary hypothyroidism) an exaggerated TSH response to TRH can be found. In cases of overt primary hypothyroidism the initial TSH value before TRH administration is elevated. Under an antithyroid drug therapy of thyrotoxicosis a lag of weeks or even months can be observed between normalisation of serum hormone values together with clinical remission of symptoms and the normalisation of the TRH induced TSH release. The cause of this discrepancy has not yet been fully clarified.

In conclusion, the TRH test is a very useful tool for the diagnosis of overt or subclinical thyroid dysfunctions. More information can be gained than by the radioiodine uptake test, and the TRH test is much easier to perform and does not lead to greater discomfort for the patients. The test is of limited value, however, for the detection and differentiation of secondary hypothyroidism or for the control of the therapeutic effect during antithyroid drug therapy.